
Sphingosine phosphate lyase regulates myogenic differentiation via S1P receptor-mediated effects on myogenic microRNA expression.

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Public Summary:

S1P lyase (SPL) catalyzes the irreversible degradation of sphingosine-1-phosphate (S1P), a bioactive lipid whose signaling activities regulate muscle differentiation, homeostasis, and muscle stem cell activation. By regulating S1P levels, SPL also controls muscle stem cell recruitment and muscle regeneration, representing a potential therapeutic target for muscular dystrophy. We found that SPL is induced during myoblast differentiation. Mouse myoblast cells lacking SPL accumulated intracellular and extracellular S1P and failed to form myotubes under conditions that normally stimulate muscle differentiation. We also showed that the S1P/SPL/S1P-receptor axis regulates the expression of a number of miRNAs associated with myogenesis, thereby contributing to muscle cell differentiation.

Scientific Abstract:

S1P lyase (SPL) catalyzes the irreversible degradation of sphingosine-1-phosphate (S1P), a bioactive lipid whose signaling activities regulate muscle differentiation, homeostasis, and satellite cell (SC) activation. By regulating S1P levels, SPL also controls SC recruitment and muscle regeneration, representing a potential therapeutic target for muscular dystrophy. We found that SPL is induced during myoblast differentiation. To investigate SPL's role in myogenesis at the cellular level, we generated and characterized a murine myoblast SPL-knockdown (SPL-KD) cell line lacking SPL. SPL-KD cells accumulated intracellular and extracellular S1P and failed to form myotubes under conditions that normally stimulate myogenic differentiation. Under differentiation conditions, SPL-KD cells also demonstrated delayed induction of 3 myogenic microRNAs (miRNAs), miR-1, miR-206, and miR-486. SPL-KD cells successfully differentiated when treated with an S1P1 agonist, S1P2 antagonist, and combination treatments, which also increased myogenic miRNA levels. SPL-KD cells transfected with mimics for miR-1 or miR-206 also overcame the differentiation block. Thus, we show for the first time that the S1P/SPL/S1P-receptor axis regulates the expression of a number of miRNAs, thereby contributing to myogenic differentiation.

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